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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/595,807	05/12/2006	Michael Howard Block	101256-1P US	6998

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EXAMINER

RAO, DEEPAK R

ART UNIT	PAPER NUMBER
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1624

MAIL DATE	DELIVERY MODE
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08/25/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/595,807	Applicant(s) BLOCK ET AL.	
	Examiner Deepak Rao	Art Unit 1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01 June 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-13, 18-21 and 28 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-13, 18-21 and 28 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Claims 1-13, 18-21 and 28 are pending in this application.

Election/Restrictions

Applicant's election of Group I in the reply filed on June 1, 2009 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18-20 and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating breast cancer, does not reasonably provide enablement for a method of inhibiting Trk activity; a method for producing an anti-proliferative effect in a warm-blooded animal in need of such treatment; or a method for the treatment or the **prophylaxis** of cancer generally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The

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nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that “undue experimentation” would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The instant claim 20 is drawn to ‘a method for producing an anti-proliferative effect’; claim 18 is directed to ‘a method of inhibiting Trk activity’; and claims 19 and 28 are drawn to ‘a method for the treatment or **prophylaxis** of cancer’. The specification at pages 2-3 provides a wide variety of conditions for which the instant compounds may be used as therapeutic agents. The specification at pages 128-129 provides *in vitro* assays to measure the TrkB kinase inhibition activity. Based on the inhibition activity, the specification provides that the compounds are useful as inhibitors of Trk, and therefore useful in the treatment of a variety of diseases, including all types of cancer. The instant claims appear to be 'reach through' claims. Reach through claims, in general have a format drawn to mechanistic, receptor binding or enzymatic functionality and thereby reach through any or all diseases, disorders or medical conditions, for which they lack written description and enabling disclosure in the specification thereby requiring undue experimentation for one of skill in the art to practice the invention.

The test data provided in the specification on pages 128-129 is related to inhibition of TrkB kinase, the instant claims on the other hand are drawn to 'method for the treatment or prophylaxis of cancer'; ‘a method of inhibiting Trk activity’; and 'a method of producing anti-proliferative effect'. Following the test procedures, the specification provides IC₅₀ data for a few

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of the exemplified compounds. Applicant did not state on record or provide any guidance that the assays provided are correlated to the clinical efficacy of the treatment of various disorders of the claims. As can be seen from specification, the *in vitro* activity data holds significant role in determining the dosage regimen based on the minimal effective concentration of each of the compound to achieve the desired inhibition of Trk.

The instant claims include: ‘a method for producing an anti-proliferative effect’; ‘a method for treatment or **prophylaxis** of cancer’; and ‘a method of inhibiting Trk activity’. The use disclosed in the specification is as Trk inhibitors, in the treatment of a large list of diseases, which include for example, cancer. There is nothing in the disclosure regarding how the disclosed *in vitro* data correlates to the treatment of the various disorders encompassed by the instant claims. The diseases encompassed by the instant claims include various types of cancer, some of which have been proven to be extremely difficult to treat. Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

Further, the instant claims recite ‘a method of inhibiting Trk activity’; ‘a method for producing anti-proliferative effect’; and ‘a method for the treatment or **prophylaxis** of cancer’, and thereby encompasses a method treating of a large list of diseases due to that activity (some of which are disclosed in the specification at pages 2-3), and there is no disclosure regarding how all these assorted types diseases are treated. See MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art. Receptor activity is

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generally unpredictable and highly structure specific area. It is inconceivable as to how the claimed compounds can treat the large list of diseases embraced by the claims having diverse mechanisms.

The instant claims include 'treating or **preventing** cancer'. A 'cancer' or 'tumor growth' is anything that causes abnormal tissue growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Thus, such term covers not only all cancers, but also covers precancerous conditions such as lumps, lesions, polyps, etc. No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of oncology. The state of the art is not indicative any pharmaceutical agents that are useful in the treatment of cancer generally. Cecil Textbook of Medicine states that "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Also see *In re Buting*, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally.

The diagnosis of each of the disease is generally suggested by medical history and reports of endoscopy, cytology, X-ray, biopsy, etc. depending on the symptoms, signs and

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complications, which is essential to establish the dosage regimen for appropriate treatment or prevention. The disclosure does not provide any guidance towards the dosage regimen required to facilitate the treatment and/or inhibition of the claimed disorders, nor indicate competent technical references in the appropriate methods.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, “the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved”. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Further, the instant claims are drawn not only to 'a method for treatment' but also to '**a method for prophylaxis** (or prevention)', for which the specification does not provide sufficient enablement. 'To prevent' actually means *to anticipate or counter in advance, to keep from happening etc.* (as per Webster's II Dictionary) and therefore it is not understood how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the recited effect of **prevention**. Based on the inhibitory activity, the instant compounds are disclosed to be useful in the “prevention” of, for example, degenerative disorders, for which applicants provide no competent evidence. It is inconceivable from the *in vitro* data of a small number of representative compounds can be correlated to the “treating or **preventing**” of the various claimed disorders, such that the claimed compounds can not only treat but also “prevent” a myriad of diseases associated with the stated activity. Further, there is no evidence on record which demonstrates that the *in-vitro* screening

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test relied upon is recognized in the art as being reasonably predictive of success in any of the contemplated areas of “preventing”. Such a reasonable correlation is necessary to demonstrate such utilities. See *Ex parte Stevens*, 16 USPQ 2d 1379 (BPAI 1990); *Ex parte Busse et al.*, 1 USPQ 2d 1908 (BPAI 1986) (the evidence must be accepted as “showing” such utility, and not “warranting further study”).

Part of the difficulty of developing drugs effective for **preventing** any of the medical conditions such as cancers, tumors, etc. lies in the lack of understanding as to why people come down with these disorders and the numerous causes of these disorders.

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

MPEP § 2164.01(a) states that “A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)”. That conclusion is clearly justified here and undue experimentation will be required to practice the claimed invention.

Thus, factors such as “sufficient working examples”, “the level of skill in the art” and “predictability”, etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have

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to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 20, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

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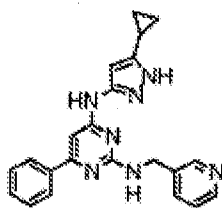
invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1. Claims 1-13, 18-21 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barlaam et al., WO 03/048133 (published June 12, 2003). The reference teaches a generic group of pyrimidine-2,4-diamine compounds, which embraces applicant's instantly claimed compounds. See formula (I) in page 3, and the compounds of the examples, specifically compounds 44, 45, 92-98, etc. The compounds are taught to be useful as pharmaceutical agents for the treatment of proliferative and hyperproliferative diseases/conditions which include cancers, see page 18. The instant claims exclude the reference disclosed specific compounds, see the proviso statement in the claims. The instant claims, however, include compounds that are structurally analogous to the reference disclosed compounds, i.e., for example structural isomers, for example, a compound wherein the pyridinyl group is attached through the 4-position as compared to the 2- or 3-position disclosed for the reference compounds. The instant claims, therefore, differ from the reference by reciting specific species or a more limited subgenus than the reference. It would have been obvious to one having ordinary skill in the art at the time of the invention to select any of the species of the genus taught by the reference, including those instantly claimed, because the skilled chemist would have the reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as taught for the genus as a whole i.e., as therapeutic agents. One of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole. It has been held that a prior art disclosed genus of useful compounds is sufficient to render prima facie obvious a species

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falling within a genus. *In re Susi*, 440 F.2d 442, 169 USPQ 423, 425 (CCPA 1971), followed by the Federal Circuit in *Merck & Co. v. Biocraft Laboratories*, 847 F.2d 804, 10 USPQ 2d 1843, 1846 (Fed. Cir. 1989).

2. Claims 1-13, 18-21 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bebbington et al., WO 2002/50065. The reference teaches a generic group of pyrimidine-thiazole compounds that are structurally analogous to applicant's instantly claimed compounds. See the compounds of structural formula I in page 6; the preferred embodiment of formula IIIc in page 135; and the specific compound IIIc-5 (page 142, structure depicted below for convenience).



IIIc-5

The compounds are taught to be useful as protein kinase inhibitors useful as pharmaceutical therapeutic agents for cancer, etc., see the abstract. The instantly claimed compounds, analogous to the reference compounds, contain a substituent $\text{-NH-CH}_2\text{-pyridinyl}$ at the 2-position of the pyrimidine ring. The instantly claimed compounds differ by having an additional substituent R^2 on the side chain is recited to be a non-hydrogen substituent, which includes an alkyl group, e.g., methyl. The reference, however, generically teaches that the alkylidene chain to be optionally substituted. For example, the instant claims differ from the reference disclosed compounds by having a methyl substituent in place of hydrogen disclosed for reference compound. It would

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have been obvious to one having ordinary skill in the art at the time of the invention to modify the reference compounds to prepare the structural analogs by replacing the hydrogen with methyl. One having ordinary skill in the art would have been motivated to prepare the instantly claimed compounds because such structurally analogous compounds are expected to possess similar properties.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-13, 18-21 and 28 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-18 of U.S. Patent No. 7,521,453. Although the conflicting claims are not identical, they are not patentably distinct from each other because

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the claims substantially analogous to the compounds of the reference claims, see the claims in the reference. The instant claims exclude the reference disclosed compounds, however, include compounds that are structural analogs of the reference compounds, i.e., compounds that differ by the position of a ring (e.g., 4-pyridinyl as compared to the 2- or 3-pyridinyl for the reference disclosed compound, etc.). It would have been obvious to one having ordinary skill in the art at the time of the invention to select any of the compounds from the reference claims, including those instantly claimed, because the skilled artisan would have had the reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as taught for the genus as a whole i.e., as pharmaceutical therapeutic agents. One of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Monday-Friday from 8:00am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

**/Deepak Rao/
Primary Examiner
Art Unit 1624**

August 25, 2009